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(12) AUSTRALIAN PATENT ABSTRACT
(19) AU
(11) AU-A-16993/83

BMS-0015 FR

(54) 2-AZABICYCLO[2.2.2.]OCTANE-3-CARBOXYLIC ACID DERIVATIVES

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(21) 16993/83 (22) 19.7.83 (24) 20.7.82
(31) 3227055 (32) 20.7.82 (33) DE
(43) 26.1.84
(51)^3 C07C 103/52 C07D 453/06

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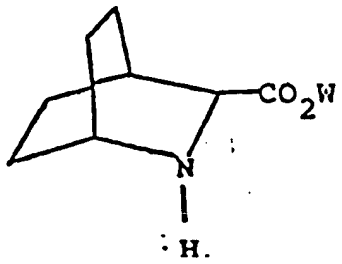
(74) WM

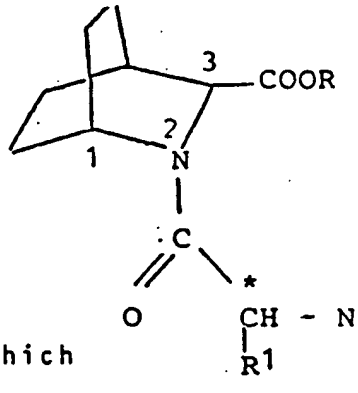
(57) Claim



(III),

Claim

1. A compound of the formula I



(I),

in which

n denotes 0 or 1,

R denotes hydrogen, (C_1 to C_6)-alkyl or aralkyl having 7 to 9 carbon atoms,

R^1 denotes hydrogen or (C_1 to C_6)-alkyl which can optionally be substituted by amino, (C_1 to C_4)-acylamino or benzoylamino, (C_2 to C_6)-alkenyl,

.../2

%105(8)/38

(C_5 to C_9)-cycloalkyl, (C_5 to C_9)-cycloalkenyl, (C_5 to C_7)-cycloalkyl-(C_1 to C_4)-alkyl, (C_6 to C_{10})-aryl or partially hydrogenated (C_6 to C_{10})-aryl, each of which can be substituted by (C_1 to C_4)-alkyl, (C_1 or C_2)-alkoxy or halogen, (C_6 to C_{10})-aryl-(C_1 to C_4)-alkyl or (C_7 to C_{11})-aroyl-(C_1 to C_4)-alkyl, both of which can be substituted, as defined above, in the aryl radical, a monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms, 1 to 2 ring atoms of which represent sulfur or oxygen atoms and/or 1 to 4 ring atoms of which represent nitrogen atoms, or an optionally protected side chain of a naturally occurring α-aminoacid,

R^2 denotes hydrogen, (C_1 to C_6)-alkyl, (C_2 to C_6)-alkenyl or (C_6 to C_{10})-aryl-(C_1 to C_4)-alkyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen and

X denotes (C_1 to C_6)-alkyl, (C_2 to C_6)-alkenyl, (C_5 to C_9)-cycloalkyl or (C_6 to C_{10})-aryl, which can be monosubstituted, disubstituted or trisubstituted by (C_1 to C_4)-alkyl, (C_1 to C_4)-alkoxy,

.../3

hydroxyl, halogen, nitro, amino, (C_1 to C_4)-alkylamino, di-(C_1 to C_4)-alkylamino and/or methylenedioxy, or denotes 3-indolyl,

and also physiologically acceptable salts thereof.

2. A compound of the formula I as claimed in claim 1, wherein the carbon atom in position 3 of the bicyclic ring system and the carbon atoms marked with a star in the side chain have the S-configuration in each case.

8. A compound of the formula III in which W has the meaning defined in claim 4.

AM page 8

Form 10

COMM NWEALTH F AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

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Complete Specification for the invention entitled:

NEW DERIVATIVES OF 2-AZABICYCLO [2.2.2]OCTANE-3-CARBOXYLIC ACID, A PROCESS FOR THEIR PREPARATION, AGENTS CONTAINING THESE DERIVATIVES AND THE USE THEREOF, AND OF 2-AZABICYCLO[2.2.2] OCTANE-3-CARBOXYLIC ACID, AS AN INTERMEDIATE STAGE AND A PROCESS FOR THE PREPARATION THEREOF

The following statement is a full description of this invention, including the best method of performing it known to :- us

aroyl-(C_1 to C_4)-alkyl, both of which can be substituted, as defined above, in the aryl radical, a monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms, 1 to 2 ring atoms of which represent sulfur or oxygen atoms and/or 1 to 4 ring atoms of which represent nitrogen atoms, or an optionally protected side chain of a naturally occurring α-aminoacid,

R^2 denotes hydrogen, (C_1 to C_6)-alkyl, (C_2 to C_6)-alkenyl or (C_6 to C_{10})-aryl-(C_1 to C_4)-alkyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen and

X denotes (C_1 to C_6)-alkyl, (C_2 to C_6)-alkenyl, (C_5 to C_9)-cycloalkyl or (C_6 to C_{10})-aryl, which can be monosubstituted, disubstituted or trisubstituted by (C_1 to C_4)-alkyl, (C_1 to C_4)-alkoxy, hydroxyl, halogen, nitro, amino, (C_1 to C_4)-alkylamino, di-(C_1 to C_4)-alkylamino and/or methylenedioxy, or denotes 3-indolyl,

and also physiologically acceptable salts thereof.

Suitable salts are, in particular, alkali metal and alkaline earth metal salts, salts with physiologically acceptable amines and salts with inorganic or organic acids, such as, for example, HCl, HBr, H_2SO_4, maleic acid or fumaric acid.

Here and in the following text, aryl is to be understood as meaning preferably optionally substituted phenyl or naphthyl, and aroyl is to be understood as

meaning preferably optionally substituted benzoyl or naphthoyl. Alkyl can be linear or branched.

A monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms, 1 to 2 ring atoms of which represent sulfur or oxygen atoms and/or 1 to 4 ring atoms of which represent nitrogen atoms, is to be understood as meaning, for example, thienyl, benzo[b]thienyl, furyl, pyranyl, benzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, isoindolyl, indolyl, purinyl, quinolizinyl, isoquinolinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolyl, cinnolinyl, pteridinyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl. These radicals can also be partially or completely hydrogenated.

Examples of naturally occurring α-aminoacids are Ala, Val, Len, Ile, Phe, Ser, Thr, Lys, Hyl, Arg, Asp, Asn, Glu, Gln, Cys, Met, Tyr, Pro, Hyp, Trp, His, Orn and Cit.

If R^1 represents a protected side chain of a naturally occurring α-aminoacid, such as, for example, protected Ser, Thr, Asp, Asn, Glu, Gln, Arg, Lys, Hyl, Cyl, Orn, Cit, Tyr, Trp, His or Hyp, preferred protective groups are the groups which are customary in peptide chemistry (cf. Houben-Weyl, Volume XV/1 and XV/2). If R^1 denotes the protected lysine side chain, the known amino protective groups are preferred, particularly, however, $(C_1 - C_6)$-alkanoyl. O-protective groups which are preferred for tyrosine are methyl or ethyl.

Compounds of the formula I contain chiral carbon

atoms in the C-3 position and also in the carbon atoms marked with a star in the side chains. The invention relates to both the R-configurations and the S-configurations at all the centers. The compounds of the formula 1 can, therefore, exist as optical isomers, as diasterecmers, as racemates or as mixtures thereof. Preferred compounds of the formula I are, however, those in which the carbon atom 3 in the bicyclic ring system, and also the carbon atoms marked with a star (*) in the side chain, have the S-configuration.

Compounds of the formula I which are particularly preferred are those in which

n denotes 1,

R denotes hydrogen or alkyl having 1 to 4 carbon atoms,

R^1 denotes hydrogen, (C_1 to C_3)-alkyl, the optionally acylated side chain of lysine, (C_2 or C_3)-alkenyl, the O-(C_1 to C_6)-alkylated side chain of tyrosine, benzyl, phenethyl, 4-aminobutyl or benzoylmethyl,

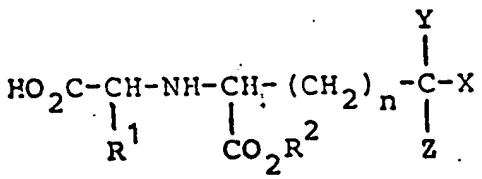
R^2 denotes hydrogen, (C_1 to C_4)-alkyl or benzyl and

X denotes cyclohexyl or phenyl which can be monosubstituted or disubstituted or, in the case of methoxy, trisubstituted by (C_1 or C_2)-alkyl, (C_1 or C_2)-alkoxy, hydroxyl, fluorine, chlorine, bromine, amino, (C_1 to C_4)-alkylamino, di-(C_1 to C_4)-alkylamino, nitro and/or methylenedioxy,

in particular compounds of the formula I in which n

denotes 1, R denotes hydrogen, R^1 denotes methyl and R^2 denotes hydrogen or ethyl, and the chiral carbon atoms which are marked with a star (*) and carbon atom 3 have the S-configuration.

The invention also relates to a process for the preparation of the compounds of the formula I. One process variant comprises reacting, in accordance with methods of amide formation which are known in peptide chemistry, a compound of the formula II

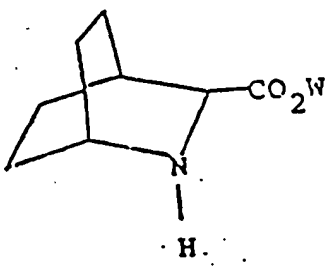


(II),

in which

n, R^1, R^2, X, Y and Z have the same meanings as in formula I,

with a compound of the formula III



(III),

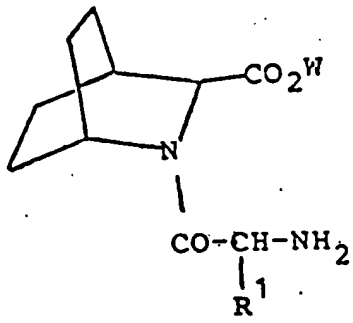
in which

W denotes hydrogen or a radical which can be split off under acid conditions or by hydrogenolysis, in particular a tert.-butyl radical or a benzyl radical,

and, if appropriate, subsequently splitting off the radical W by treatment with acid or hydrogenation and, if appropriate, also splitting off the radical R2 by addi-

tional treatment with acids or bases, the free carboxylic acids being obtained in each case.

Further processes of synthesis for the preparation of the compounds of the formula I in which Y and Z together denote oxygen consist in reacting, in a known manner, in a Michael reaction (Organikum, 6th edition, page 492, 1967), a compound of the formula IV



(IV),

in which

R^1 has the same meaning as in formula I and

W has the same meaning as in formula III,

with a compound of the formula V

$$R^2O_2C\text{-}CH{=}CH\text{-}CO\text{-}X \qquad (V),$$

in which

R^2 and X have the same meanings as in formula I, and, if appropriate, splitting off the radical W and/or the radical R^2 as described above, or in reacting, in a known manner, in a Mannich reaction (Bull. Soc. Chim. France 1973, page 625), a compound of the abovementioned formula IV with a compound of the general formula VI in which R^2 has the same meaning as in formula I and with a compound of the general formula VII

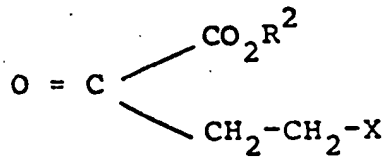
$$OHC\text{-}CO_2R^2 \quad (VI) \qquad X\text{-}CO\text{-}CH_3 \quad (VII),$$

in which

X has the same meaning as in formula I,

and, if appropriate, subsequently splitting off the radical W and/or the radical R^2 as described above, with the formation of the free carboxyl groups.

Compounds of the formula I in which Y and Z are each hydrogen can also be prepared by reacting a compound of the formula IV mentioned above, in accordance with the procedure described in J. Amer. Chem. Soc. 93, 2897 (1971), with a compound of the formula VIII



(VIII),

in which

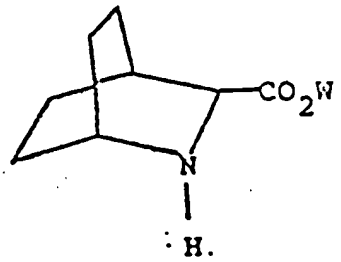
R^2 and X have the same meanings as in formula I, reducing the resulting Schiff's bases and then, if appropriate, splitting off the radical W and/or the radical R^2 as described above, with the formation of the free carboxyl groups. The reduction of the Schiff's bases can be effected electrolytically or by means of a reducing agent, such as, for example, sodium borohydride or sodium cyanoborohydride.

Compounds of the formula I in which Y is hydroxyl and Z is hydrogen can also be obtained, for example, by reducing a compound I which has been obtained in accordance with the above procedures and in which Y and Z together are oxygen. This reduction can be effected by means of a reducing agent, such as sodium borohydride and other complex boranates or, for example, borane-amine complexes.

Compounds of the formula I in which R represents hydrogen can, if appropriate, be converted by methods

known per se into their esters of the formula I in which R denotes (C_1 to C_6)-alkyl or (C_7 to C_9)-aralkyl.

The invention also relates to compounds of the formula IlI



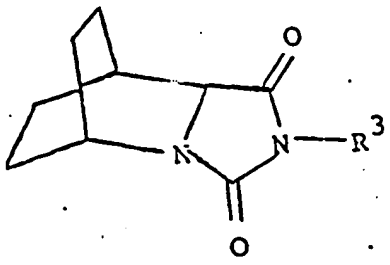
(III),

in which

W denotes hydrogen or a radical which can be split off under acid conditions or by hydrogenolysis, such as tert.-butyl or benzyl.

These compounds are used, in accordance with the invention, as starting materials in the synthesis of compounds of the formula I and can be prepared in accordance with the invention

a) by saponifying a compound of the formula IX



(IX),

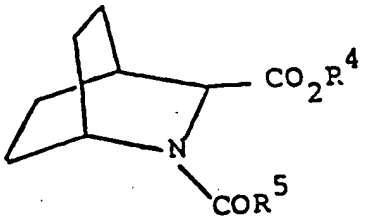
in which

R^3 represents a (C_1 to C_6)-alkyl, aryl-(C_1 to C_3)-alkyl, phenyl, 4-methoxyphenyl or 4-chlorophenyl radical, in particular a methyl, benzyl, phenyl or 4-chlorophenyl radical,

by means of an alkali metal hydroxide or alkaline earth metal hydroxide, in particular barium hydroxide, at 20 to 150oC, in particular at 60 to 120oC, in water or mixtures

thereof with an organic solvent, such as methanol, ethanol, isopropanol, tetrahydrofuran or dioxane, and, if appropriate, esterifying the resulting aminoacid (III/W = hydrogen) in accordance with customary methods of aminoacid chemistry, or

b) by reacting a compound of the formula X



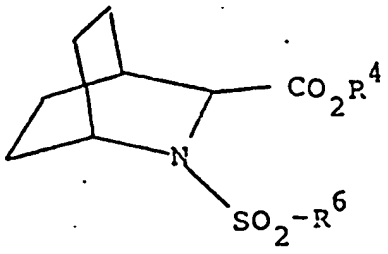
(X),

in which

R^4 denotes a (C_1 to C_6)-alkyl or aryl-(C_1 to C_3)-alkyl radical, in particular a methyl, ethyl or benzyl radical, and R^5 denotes a phenyl, methyl, (C_1 to C_4)-alkoxy or aryl-(C_1 to C_3)-alkoxy radical,

under the conditions of variant a) with an alkali metal hydroxide or alkaline earth metal hydroxide, and, if appropriate, esterifying the resulting aminoacid (III/W = hydrogen), or

c) by reacting a compound of the formula XI



(XI),

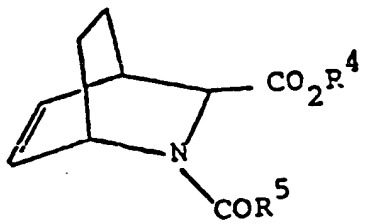
in which

R^4 has the same meaning as in formula X and

R6 represents a phenyl, 4-methylphenyl or 4-chlorophenyl radical,

first with an alkali metal or alkaline earth metal, in particular s dium or calcium, in liquid ammonia at -60° to -10°, in particular at -40 to -20°C, and then with an alkali metal hydroxide or alkaline earth metal hydroxide, in particular sodium hydroxide, potassium hydroxide or barium hydroxide, at 20° to 120°C, in particular 60 to 100°C, and, if appropriate, esterifying the product, or reversing the sequence of the reaction stages described.

Compounds of the formula lx are known from Tetrahedron 27, page 3119 (1971); compounds of the formula X are obtained readily from the dehydro compounds of the formula XII

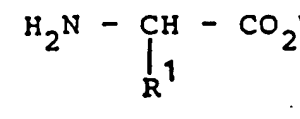


(XII),

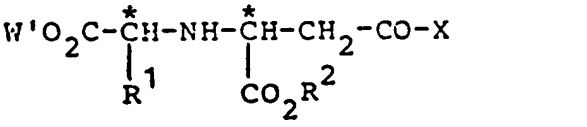
which are known from J. Chem. Soc. Perkin I, page 2343 (1977), by hydrogenation in an organic solvent, for example ethyl acetate, in the presence of a catalyst, for example palladium on animal charcoal. Compounds of the formula XI are similarly obtained by hydrogenation, in the manner just described, from the compounds which are known from Chem. Ber. 98, page 1431 (1965).

The compounds of the formula II in which n is 1, Y and Z is hydrogen, R^1 is methyl and R^2 is methyl or ethyl and X is phenyl and which are used as starting materials for the preparation of the compounds of the formula I are known EP-A-No. 37,231). The compounds of the formula II can be prepared by various procedures. One variant of the synth sis starts from a

ketone of the formula VII mentioned above, which is reacted, in accordance with known procedures in a Mannich reaction, with a compound of the formula VI mentioned above together with aminoacid esters of the formula XIII



(XIII)



(XIV),

in which

R^1 has the meaning mentioned above and

W' denotes a radical which can be split off by hydrogenolysis or under acid conditions, in particular a benzyl radical or a tert.-butyl radical,

to give a compound of the formula XIV in which

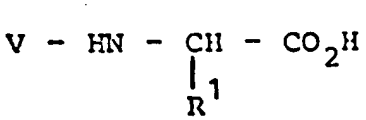
R^1, R^2, X and W' have the meanings mentioned above, subject to the limitation that, if W' denotes a radical which can be split off by hydrogenolysis, in particular benzyl, R^2 must not have the meaning of W'.

If the radical W' is split off by hydrogenolysis with the aid of, for example, palladium, compounds of the formula II in which Y and Z are hydrogen are obtained at a hydrogen absorption of 3 mole equivalents. Stopping the hydrogen absorption at 1 mole equivalent gives compounds of the formula II in which n is 1 and Y and Z together are oxygen, which are also obtained if the radical W' in the formula XIV is split off by means of acids, such as, for example, trifluoroacetic acid or hydrochloric acid, in an inert organic solvent, such as, for example, dioxane.

Compounds of the formula XIV are also accessible in accordance with known procedures by Michael addition reactions between a compound of the abovementioned formula V and a compound of the abovementioned formula XIII. This process is preferentially suitable for the preparation of compounds of the formula XIV in which R^1 denotes methyl, R^2 denotes ethyl and X denotes aryl.

The compounds of the formula XIV are obtained in the form of mixtures of diastereomers. Diastereomers of the formula XIV which are preferred are those in which the chiral carbon atoms marked with a star have the S-configuration in each case. These diastereomers can be resolved, for example, by crystallization or by chromatography, for example over silica gel. The configurations of the chiral carbon atoms are retained when the radical W' is subsequently split off.

The compounds of the abovementioned formula IV which are used as starting materials for the preparation of the compounds of the formula I are obtained in accordance with known procedures from the compounds of the formula III mentioned above by reacting the latter with an N-protected 2-aminocarboxylic acid of the formula XV



(XV),

in which

V is a protective group and

R^1 has the meaning mentioned above.

An example of a suitable protective group V, which is split off again when the reaction is complete, is

tert.-butoxycarbonyl.

The reaction of a compound of the formula II with a compound of the formula III in order to prepare a compound of the formula I is effected in accordance with a condensation reaction which is known in peptide chemistry, dicyclohexylcarbodiimide and 1-hydroxybenzotriazole, for example, being added as the condensation agent. Trifluoroacetic acid or hydrogen chloride are preferably employed as acids when the radical W is subsequently split off under acid conditions.

The compounds of the formula III which are obtained in accordance with the procedure described above are produced in the form of a mixture and can be separated from one another, for example by recrystallization or by chromatography.

The compounds of the formula III are produced in the form of racemic mixtures and can be employed as such in the further syntheses described above. However, they can also be employed in the form of pure enantiomers after the racemates have been resolved into the optical antipodes by means of customary methods, for example via the formation of salts with optically active bases or acids.

If the compounds of the formula I are produced in the form of racemates, these can also be split into their enantiomers by the customary methods, such as, for example, via the formation of salts with optically active bases or acids, or can be separated by chromatography.

The compounds, according to the invention, of the formula I are present in the form of internal salts if R

is hydrogen. As amphoteric compounds, they can form salts with acids or with bases. These salts are prepared in a customary manner by reaction with one equivalent of acid or base.

The compounds of the formula I and their salts possess an intense hypotensive action of long duration. They are powerful inhibitors of the angiotensin converting enzyme (ACE-inhibitors). They can be employed for combating high blood pressure of various origins. It is also possible to combine them with other hypotensive or vasodilative compounds or compounds having a diuretic action. Typical representatives of these categories of active compounds are described, for example, in Erhardt-Ruschig, Arzneimittel ("Medicaments"), 2nd edition, Weinheim, 1972. Administration can be effected intravenously, subcutaneously or perorally.

The dosage for oral administration is 1-100 mg, preferably 1-40 mg, per individual dose for an adult patient of normal weight; this corresponds to about 15-1300 µg/kg/day, preferably 15-500 µg/kg/day. In severe cases, the dosage can also be increased, since toxic properties have not hitherto been observed. It is also possible to reduce the dose, and this is expedient above all if diuretics are administered at the same time.

The compounds according to the invention can be administered orally or parenterally in an appropriate pharmaceutical formulation. For an oral administration form, the active compounds are mixed with the additives customary for this purpose, such as excipients, stabil-

izers or inert diluents, and are converted by customary methods into suitable administration forms, such as tablets, dragees, dry-filled capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. Examples of inert excipients which can be used are gum arabic, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. The products can be formulated either as dry granules or as moist granules. Examples of suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil.

For subcutaneous or intravenous administration, the active compounds or physiologically acceptable salts thereof are converted into a solution, suspension or emulsion, if desired together with the substances customary for this purpose, such as solubilizers, emulsifiers or further auxiliaries. The following are examples of suitable solvents for the new active compounds and the corresponding physiologically acceptable salts: water, physiological sodium chloride solutions or alcohols, for example ethanol, propanediol or glycerol, and also sugar solutions, such as solutions of glucose or mannitol, or a mixture of the various solvents mentioned.

The extremely high activity of the compounds according to formula I is demonstrated by the pharmacological data in the following tables:

Intraduodenal administration to narcotized rats, 50% inhibition of the presso reaction initiated by 310 ng of angiotensin I 30 minutes after administration in a

dose of ..... = ED_{50}:

Table

(The compounds listed possess the S-configuration at all the asymmetric carbon atoms)

n	X	Y	Z	R^1	R^2	R	ED_{50} (µg/kg)
1	C_6H_5	H	H	C_2H_5	CH_3	H	30
1	C_6H_5	H	H	H	CH_3	H	600
1	C_6H_5	- O -		C_2H_5	CH_3	H	340

The symbols n, X, Y, Z, R, R^1 and R^2 relate to the compounds of the formula I.

The examples which follow serve to illustrate the invention without limiting it to the compounds mentioned as representatives.

Unless otherwise specified, the 1H-NMR data quoted in the following examples were determined by measurement in $CDCl_3$ and are quoted in δ (ppm).

Example 1

Benzyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

a) N-(p-chlorophenyl)-2-azabicyclo[2.2.2]oct-5-ene-2,3-dicarboximide

A mixture of 11.4 ml of cyclohexadiene, 7.2 g of 3-(p-chlorophenyl)-5-methoxyimidazoline-2,4-dione, 6 ml of trifluoroacetic acid and 135 ml of toluene is heated at 100°C for 18 hours. After the mixture has been cooled and concentrated, it is chromatographed over silica gel using 1:2 ethyl acetate/cyclohexane as the mobile phase. 1.8 g of pale yellow crystals of melting point

171°C are obtained.

1H-NMR data:

7.7 - 7.1 (m, 4H);

6.6 - 6.1 (m, 2H);

4.7 - 4.45 (m, 1H);

4.21 (d, J = 2 Hz, 1H);

3.3 - 3.0 (m, 1H);

2.4 - 1.0 (m, 4H).

b) N-(p-chlorophenyl)-2-azabicyclo[2.2.2]octane-2,3-dicarboximide

1.8 g of N-(p-chlorophenyl)-2-azabicyclo[2.2.2]-oct-5-ene-2,3-dicarboximide in 30 ml of ethyl acetate, with the addition of 100 mg of 10% strength palladium on animal charcoal, are hydrogenated at room temperature and normal pressure. Filtration and concentration gives 1.8 g of pale yellow crystals of melting point 189°C.

1H-NMR data:

7.40 (s, 4H);

4.2 - 3.9 (m, 2H);

2.6 - 1.1 (m, 9H).

c) 2-azabicyclo[2.2.2]octane-3-carboxylic acid

1.8 g of N-(p-chlorophenyl)-2-azabicyclo[2.2.2]-octane-2,3-dicarboximide are added to 6.4 g of barium hydroxide octahydrate in 30 ml of dioxane and 30 ml of water, and the mixture is boiled under reflux for 16 hours. The mixture is diluted with 60 ml of water and neutralized by adding solid carbon dioxide, the precipitate is filtered off with suction and the filtrate is extracted with ether. The aqueous phase is concentrated to dryness, the residue is

taken up in a little isopropanol and the product is precipitated with diisopropyl ether. 0.9 g of a colorless, amorphous powder is obtained.

1H-NMR data (D_2O):

3.9 - 3.6 (m, 1H);

2.8 - 2.6 (m, 1H);

2.0 - 1.3 (m, 9H);

Mass spectroscopy: 155 (M^+, 5%); 110 (M^+-COOH, 100%); 82 (75%)

d) benzyl-2-azabicyclo[2.2.2]octane-3-carboxylate

0.9 g of 2-azabicyclo[2.2.2]octane-3-carboxylic acid is added at -5°C to a mixture, prepared at -20°C, of 0.9 ml of thionyl chloride and 9 ml of benzyl alcohol. When the mixture has warmed up to room temperature it is allowed to stand for 16 hours, the benzyl alcohol is removed by distillation, the residue is stirred three times with diisopropyl ether and taken up in 5% strength sodium carbonate solution, the solution is extracted three times with methylene chloride and the extracts are dried over potassium carbonate and concentrated. 0.5 g of a pale yellow oil is obtained.

1H-NMR data:

7.1 (s, 5H);

5.0 (s, 2H);

3.9 - 3.7 (m, 1H);

2.8 - 2.6 (m, 1H);

2.0 - 1.3 (m, 9H).

e) Benzyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate (diastereomer A1) and

Benzyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-R-carboxylate (diastereomer B1)

0.57 g of N-(1-S-carboethoxy-3-phenylpropyl)-S-alanine, 0.27 g of N-hydroxybenzotriazole, 0.57 g of benzyl 2-azabicyclo[2.2.2]octane-3-carboxylate and 0.41 g of dicyclohexylcarbodiimide are dissolved in 4 ml of dimethylformamide at room temperature, and the solution is stirred for 1 hour. It is diluted with ethyl acetate, the precipitated dicyclohexylurea is filtered off and the filtrate is washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated. The resulting oil is chromatographed over silica gel using 1:1 cyclohexane/ethyl acetate as the mobile phase in order to separate the diastereomers.

Diastereomer A1: 0.27 g, R_f value: 0.19

1H-NMR data:

7.2 (s, 5H);

7.08 (s, 5H);

5.1 (s, 2H);

4.5 - 4.2 (m, 1H);

4.1 (q, J = 7 Hz, 2H);

3.9 - 1.3 (m, 16H);

1.4 - 1.1 (d+t, J = 7 Hz, 6H).

Diastereomer B1: 0.26 g, R_f value: 0.14

1H-NMR data:

7.2 (s, 5H);

7.05 (s, 5H);

5.05 (s, 2H);

4.5 - 4.2 (m, 1H);

4.15 (q, J = 7 Hz, 2H);

3.9 - 1.3 (m, 16H);

1.25 (d+t, J = 7 Hz, 6H).

Example 2

N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo-[2.2.2]octane-3-S-carboxylic acid hydrochloride

0.27 g of benzyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate (diastereomer A1) in 20 ml of ethanol is hydrogenated at room temperature and normal pressure using 50 mg of palladium on animal charcoal. The catalyst is filtered off, 2.5 N ethanolic hydrochloric acid is added to the filtrate and the mixture is concentrated. The resulting oil is taken up in a little methylene chloride and precipitated with isopropyl ether. A colorless powder, melting point 185-195°C (decomposition), is obtained.

1H-NMR data ($DMSO-d_6$)

7.25 (s, 5H);

4.25 (q, 2H);

4.6 - 1.4 (m, 17H);

1.38 (d, 3H, J = 7 Hz);

1.25 (t, 3H, J = 7 Hz).

Mass spectroscopy: 416 (M^+, 1.5%); 294 (19%); 248 (11%); 234 (100%).

Example 3:

N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo-[2.2.2]octane-3-R-carboxylic acid hydrochloride

0.26 g of benzyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-R-carboxylate (diastereomer B1) in 20 ml ethanol is hydrogenated at room temperature and normal pressure using 50 mg of palladium on animal charcoal as the catalyst. The catalyst is filtered off, 2.5 N ethanolic hydrochloric acid is added to the filtrate, the mixture is concentrated, toluene is added to the residue and concentration is carried out again. The crystalline residue is taken up in diisopropyl ether and filtered off with suction, melting point 196-198°C.

1H-NMR data ($DMSO-d_6$):

7.22 (s, 5H);

4.2 (q, J = 7 Hz, 2H);

4.6 - 1.4 (m, 17 H);

1.4 (d, J = 7 Hz, 3H);

1.26 (t, J = 7 Hz, 3H);

Mass spectroscopy: 416 (M^+, 0.5%); 294 (100%); 248 (56%); 234 (90%).

Example 4

Tert.-butyl 2-azabicyclo[2.2.2]octane-3-carboxylate hydrochloride

A solution of 1.1 g of 2-azabicyclo[2.2.2]octane-3-carboxylic acid in 10 ml of dioxane is cooled to -10°C and 1 ml of concentrated sulfuric acid and 5 g of isobutylene are added. The reaction mixture is slowly warmed

to 20 to 25°C in an autoclave and is stirred at this temperature for 20 hours. The mixture is poured into ice cold 50% strength aqueous sodium hydroxide and extracted with methylene chloride. The combined organic phases are washed with water, dried with sodium sulfate and concentrated, the residue is dissolved in ether and gaseous hydrogen chloride is passed into the solution. The product is filtered off with suction. 0.8 g of the title compound is obtained.

1H-NMR data ($DMSO-d_6$):

3.9 - 3.6 (m, 1H);

2.9 - 2.6 (m, 1H);

2.0 - 1.3 (m, 9H);

1.3 (s, 9H).

Example 5:

Tert.-butyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate (diastereomer A5)

0.28 of the title compound is obtained, as a colorless oil, analogously to the procedure of Example 1 from 0.5 g of tert.-butyl 2-azabicyclo[2.2.2]octane-3-carboxylate hydrochloride, 0.57 g of N-(1-S-carboethoxy-3-phenylpropyl)-S-alanine, 0.27 g of N-hydroxybenzotriazole and 0.41 g of dicyclohexylcarbodiimide, with the addition of 0.23 g of N-ethylmorpholine.

1H-NMR data:

7.1 (s, 5H);

4.5 - 4.1 (m, 1H);

4.1 (q, J = 7 Hz, 2H);

3.9 - 1.9 (m, 16 H);

1.3 (s, 9H);

1.2 (d+t, J = 7 Hz, 6H).

Example 6

N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo-[2.2.2]octane-3-S-carboxylic acid hydrochloride

0.28 g of the tert.-butyl ester from Example 5 is dissolved in 1.5 ml of trifluoroacetic acid and the mixture is stirred for 3 hours at 0°C. The trifluoroacetic acid is removed by evaporation in vacuo, toluene is added and the mixture is concentrated again. The mixture is filtered through a short silica gel column using 10:1 methylene chloride/ethanol as the mobile phase, acidified with ethanolic hydrochloric acid and concentrated. The residue is dissolved in a little methylene chloride, and the title compound is precipitated with diisopropyl ether. This gives 0.21 g of a compound identical with the compound from Example 2.

Example 7

N-(1-S-carboxy-3-phenylpropyl)-S-alanyl-2-azabicyclo-[2.2.2]octane-3-S-carboxylic acid

Two equivalents of potassium hydroxide and a 10% excess of 4N potassium hydroxide solution are added to a solution of 0.2 g of N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride in 2 ml of water. After stirring for 8 hours at 20 to 25°C, the pH of the reaction solution is adjusted to a value of 4 with 2N hydrochloric acid and the mixture is concentrated in vacuo. The residue is

taken up in ethyl acetate and the salt which has been precipitated is filtered off. The ethyl acetate solution is concentrated and the residue is triturated with diisopropyl ether and filtered off with suction.

1H-NMR data:

7.1	(s, 5H);
4.4 - 4.0	(m, 1H);
3.9 -1.3	(m, 16H);
1.2	(d, 3H).

Example 8

Tert.-butyl N-(1-S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

0.24 g of tert.-butyl 2-azabicyclo[2.2.2]octane-3-carboxylic acid hydrochloride is dissolved, together with 0.14 g of 1-hydroxybenzotriazole, 0.29 g N-(1-S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanine, 0.22 g of dicyclohexylcarbodiimide and 0.12 g of N-ethylmorpholine, in 3 ml of DMF, and the solution is stirred for 3 hours at 20°C. The mixture is diluted with ethyl acetate and filtered, and the filtrate is washed twice with water, dried and concentrated. The residue is chromatographed over silica gel using 1:1 cyclohexane/ethyl acetate as the mobile phase; 0.16 g of the title compound is obtained.

1H-NMR data:

8.2 - 7.1	(m, 5H);
4.7 - 4.1	(m, 1H);
4.1	(q, J = 7 Hz, 2H);
3.9 - 1.3	(m, 14H);
1.3	(s, 9H);

1.2 (d+t, 6H).

Example 9

N-(1-S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

0.16 g of the compound from Example 8 is reacted analogously to the process of Example 6 with 2 ml of trifluoroacetic acid to give 0.12 g of the title compound.

1H-NMR data ($DMSO-d_6$):

8.1 - 7.2 (m, 5H);
4.7 - 4.1 (m, 1H);
4.1 (q, J = 7Hz, 2H);
3.9 - 3.1 (m, 14H);
1.2 (d+t, 6H).

Example 10

N-(1-S-carboxy-3-phenyl-3-oxopropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid

0.19 g of the compound from Example 9 is reacted with 2.2 equivalents of potassium hydroxide analogously to the procedure described in Example 7.

1H-NMR data:

8.1 - 7.2 (m, 5H);
4.7 - 4.1 (m, 1H);
3.9 - 3.1 (m, 14H);
1.2 (d, J = 7 Hz, 3H).

Example 11

Tert.-butyl S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

a) tert.-butyl N-methylsulfonylethoxycarbonyl(MSC)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

6.7 g of 1-hydroxybenzotriazole and 14.0 g of tert.-butyl 2-azabicyclo[2.2.2]octane-3-carboxylate are added to a solution of 10 g of MSC-ala-OH in 50 ml of dimethylformamide. The pH is adjusted to a value of 8.0 with N-ethylmorpholine. The mixture is cooled in an ice bath and 10.5 g of dicyclohexylcarbodiimide are added. The mixture is stirred at 20 - 25°C for 15 hours. The precipitated urea is filtered off with suction, the filtrate is concentrated in vacuo and the residue is taken up in ethyl acetate. The organic phase is washed successively with potassium bisulfate solution, potassium bicarbonate solution and sodium chloride solution and is dried and evaporated. The residue is chromatographed over silica gel using 1:1 ethyl acetate/cyclohexane.

Yield: 10 g

1H-NMR data:

4.8 - 3.8 (m, 2H);

3.8 - 3.1 (m, 5H);

3.0 (s, 3H);

2.9 - 1.2 (m, 9H);

1.4 (s, 9H);

1.2 (d, J = 7Hz, 3H).

b) tert.-butyl S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

2.0 g of the compound from Example 10 a are dissolved in 15 ml of methanol and 1.5 ml of water. The pH is adjusted to 13 with 2N sodium hydroxide solution, and the mixture is stirred at room temperature for 2 hours. It is then neutralized with 2N hydrochloric acid, the

methanol is removed by evaporation in vacuo, the aqueous phase is extracted with ethyl acetate, and the ethyl acetate solution is washed with water, dried and concentrated. The residue is filtered through silica gel using ethyl acetate as the mobile phase.

Yield: 0.8 g

1H-NMR data:

4.7 - 4.2 (m, 1H);

3.9 - 3.3 (m, 2H);

2.9 - 1.2 (m, 9H);

1.4 (s, 9H);

1.2 (d, J = 7Hz, 3H).

Example 12

Tert.-butyl N-(1-S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

5 mmoles of the compound from Example 11 b are dissolved, together with 5 mmoles of ethyl 3-benzoylacrylate and 5 drops of triethylamine, in 50 ml of anhydrous ethanol, and the mixture is stirred at 20 to 25°C for 24 hours. It is evaporated to dryness and the residue is taken up in ethyl acetate. The ethyl acetate solution is then washed with water, dried and evaporated. The mixture of diastereomers is chromatographed over silica gel using ethyl acetate/cyclohexane as the mobile phase. The ^{1}H-NMR data agree with the data of the compound from Example 8.

Example 13

tert.-butyl N-(1-S-carboethoxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

5 mmoles of tert.-butyl S-alanyl-2-azabicyclo-[2.2.2]octane-3-S-carboxylate are dissolved in 15 ml of anhydrous ethanol. The pH of the solution is adjusted to 7.0 with ethanolic potassium hydroxide, and 0.7 g of pulverized molecular sieve (4 Å) followed by 5 mmoles of ethyl 2-keto-4-phenylbutyrate is added. A solution of 0.6 g of sodium cyanoborohydride in 6 ml of anhydrous ethanol is added dropwise slowly. After a reaction time of 20 hours at 20 to 25°C, the solution is filtered and the solvent is removed by distillation. The residue is taken up in ethyl acetate/water. The ethyl acetate phases are evaporated and the residue is chromatographed over silica gel using 1:4 ethyl acetate/cyclohexane.

The ^{1}H-NMR data agree with the data of the compound from Example 5.

Example 14

Tert.-butyl N-(1-S-carboethoxy-3-phenyl-3-oxopropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate

10 mmoles of acetophenone, 10 mmoles of ethyl glyoxylate and 10 mmoles of tert.-butyl S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylate in 30 ml of glacial acetic acid are heated at 45°C for 36 hours. The mixture is concentrated in vacuo, and the residue is neutralized with sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate phase is concentrated and chromatographed over silica gel using 1:1 ethyl acetate/cyclohexane as the mobile phase. The NMR data agree with the data of the compound from Example 8.

Example 15

N-(1-S-carboethoxy-3-R,S-hydroxy-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid

0.5 g of N-(1-S-carboethoxy-3-oxo-3-phenylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid is dissolved in 5 ml of aqueous ethanol and 0.1 g of sodium borohydride is added. The mixture is stirred at room temperature for 14 hours. Ethyl acetate is then added, and the ethyl acetate solution is washed with water, dried and evaporated. The crude product is filtered through silica gel using 9:1 ethyl acetate/methanol as the mobile phase.

Yield: 0.3 g.

1H-NMR data:

7.3 - 6.9 (m, 5H);
5.4 (t, 1H);
4.7 - 4.2 (m, 1H);
3.9 - 1.3 (m, 14H);
1.3 (d+t, 16H).

Example 16

2-Azabicyclo[2.2.2]octane-3-carboxylic acid

a) butyl 2-(p-toluenesulfonyl)-2-azabicyclo[2.2.2]oct-5-enecarboxylate

28 g N-[butoxycarbonylmethylene]-p-toluenesulfonamide and 10 g of cyclohexadiene in 50 ml of toluene are heated at 80°C for 12.5 hours. After cooling, the mixture is concentrated.

1H-NMR data:

7.4 - 6.9 , (m, 4H);

5.6 - 4.2 (m, 4H);

4.1 (t, J = 7Hz, 2H);

2.3 (s, 3H);

2.4 - 1.2 (m, 7H);

1.0 (t, 3H).

b) 15 g of the compound from Example 16 a in 200 ml of ethyl acetate are hydrogenated at room temperature and normal pressure using 0.5 g of 10% strength palladium on charcoal. The catalyst is filtered off and the filtrate is concentrated.

1H-NMR data

7.4 - 6.9 (m, 4H);

5.3 - 4.2 (m, 2H);

4.1 (t, 3H);

3.9 - 3.3 (m, 1H);

2.3 (s, 3H);

2.4 - 1.2 (m, 11H);

1.0 (t, 3H).

c) 2-azabicyclo[2.2.2]octane-3-carboxylic acid

4 g of the compound from Example 16 b, together with 1.2 equivalents of KOH in 20 ml of water, are warmed at 60°C for 4 hours. The mixture is neutralized with 1N HCl and concentrated. 50 ml of liquid ammonia, and sufficient sodium for the blue color to remain, are added to the residue. After 3 hours at -30°C, anhydrous sodium acetate is added until the color disappears. The ammonia is removed by evaporation and the crude product is purified on an acid ion exchanger column. The analytical data agree with those of the compound from Example 1 c.

Example 17

2-Azabicyclo[2.2.2]octane-3-carboxylic acid

a) methyl 2-benzyloxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate

4 ml of boron trifluoride-etherate are added, while stirring, to a mixture of 20.2 g of methyl N-benzyloxycarbonyl-2-methoxyglycine and 60 ml of toluene. 8 ml of cyclohexadiene in 16 ml of toluene are added dropwise at 80°C. After 1.5 hours at 80°C the mixture is cooled and poured into 100 ml of an aqueous solution of sodium bicarbonate, and the toluene phase is dried over magnesium sulfate and concentrated and the residue is chromatographed over silica gel using 2:1 petroleum ether/ether as the mobile phase. 10.6 g of the title compound are obtained in the form of an exo/endo-mixture.

b) methyl 2-azabicyclo[2.2.2]octane-3-carboxylate

5.4 g of the compound from Example 17 a in 200 ml of ethyl acetate are hydrogenated at room temperature and normal pressure using 0.5 g of palladium on animal charcoal as the catalyst. When 2 moles of hydrogen have been taken up, the catalyst is filtered off and the filtrate is concentrated.

Yield: 3.4 g.

1H-NMR data:

3.9 (s, 3H);

3.8 - 3.5 (m, 1H);

2.9 - 2.6 (m, 1H);

2.0 - 1.3 (m, 9H).

The following compounds were also prepared by the

processes described in Examples 1 e and 2, using the appropriate starting materials:

Example 18

N-(1-S-carboethoxy-3-cyclohexylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	4.2	(q, 2H)
	4.6 - 1.4	(m, 28H)
	1.4	(d, 3H, J = 7Hz)
	1.25	(t, 3H, J = 7Hz)

m/e: 422(M^+, 1%)

Example 19

N-(1-S-carboethoxy-3-cyclopentylpropyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	4.25	(q, 2H)
	4.5 - 1.4	(m, 26H)
	1.35	(d, 3H, J = 7Hz)
	1.28	(t, 3H, J = 7Hz)

m/e: 408 (M^+, 1%)

Example 20

N-(1-S-carboethoxy-4,4-dimethylpentyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	4.2	(q, 2H)
	4.6 - 1.4	(m, 17H)
	1.32	(t, 3H, J = 7Hz)
	1.25	(d, J = 7Hz, 3H)
	1.05	(s, 9H)

m/e: 396 (M^+, 1.7%)

Example 21

N-(1-S-carboethoxy-3-(2,6-dimethylphenyl)-propyl)-S-alanyl-

2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.3 - 7.0	(m, 3H)
	4.25	(q, 12H)
	4.6 - 1.4	(m, 17H)
	2.3	(s, 6H)
	1.35	(d, J = 7Hz, 3H)
	1.32	(t, J = 7Hz, 3H)

m/e: 444 (M^+, 1.2%)

Example 22

N-(1-S-carboethoxy-3-(4-methoxyphenyl)-propyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.1 - 6.5	(m, 4H)
	4.25	(q, 2H)
	4.6 - 1.5	(m, 17H)
	3.6	(s, 3H)
	1.3	(d+t, 6H)

m/e: 446 (M^+, 0.4%)

Example 23

N-(1-S-carboethoxy-3-(3,4-dimethoxyphenyl)-propyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.0 - 6.3	(m, 3H)
	4.2	(q, 2H)
	4.5 - 1.4	(m, 17H)
	3.7	(s, 6H)
	1.3	(d+t, 6H)

m/e: 476 (M^+, 0.6%)

Example 24

N-(1-S-carbocthoxy-3-(4-fluorophenyl)-propyl)-S-alanyl-

2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.3 - 6.9	(m, 4H)
	4.3	(q, 2H)
	4.4 - 1.4	(m, 17H)
	1.35	(t, J = 7Hz, 3H)
	1.2	(d, J = 7Hz, 3H)

m/e: 434 (M^+, 0.7%)

Example 25

N-(1-S-carboethoxy-3-(2,6-dichlorophenyl)-propyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.4 - 7.0	(m, 3H)
	4.2	(q, 2H)
	4.5 - 1.4	(m, 17H)
	1.3	(d+t, 6H)

m/e: 484 (M^+, 0.2%)

Example 26

N-(1-S-carboethoxy-3-(3,4-methylenedioxyphenyl)-propyl)-S-alanyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.0 - 6.2	(m, 3H)
	4.25	(q, 2H)
	5.0	(s, 2H)
	4.4 - 1.5	(m, 17H)
	1.3	(d+t, 6H)

m/e: 460 (M^+, 0.4%)

Example 27

N-(1-S-carboethoxy-3-phenylpropyl)-O-ethyl-S-tyrosyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):	7.2 - 6.5	(m, 9H)

	4.2	(q, 2H)
	4.3 - 1.4	(m, 21H)
	1.3	(2t, 6H)

m/e: 536 (M^+, 0.3%)

Example 28

N-(1-S-carboethoxy-3-phenylpropyl)-O-methyl-S-tyrosyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):		
	7.2 - 6.4	(m, 9H)
	4.2	(q, 2H)
	4.3 - 1.4	(m, 19H)
	2.3	(s, 3H)
	1.3	(t, 3H)

m/e: 522 (M^+, 0.1%)

Example 29

N-(1-S-carboethoxy-3-cyclohexylpropyl)-O-ethyl-S-tyrosyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):		
	7.2 - 6.5	(m, 4H)
	4.25	(q, 2H)
	4.3 - 4.14	(m, 32H)
	1.3	(2t, 6H)

m/e: 542 (M^+, 0.2%)

Example 30

N-(1-S-carboethoxy-3-cyclohexylpropyl)-S-lysyl-2-azabicyclo[2.2.2]octane-3-S-carboxylic acid hydrochloride

1H-NMR data (DMSO-d_6):		
	4.2	(q, 2H)
	4.3 - 1.4	(m, 39H)
	1.3	(t, 3H)

m/e: 479 (M^+, 0.1%)

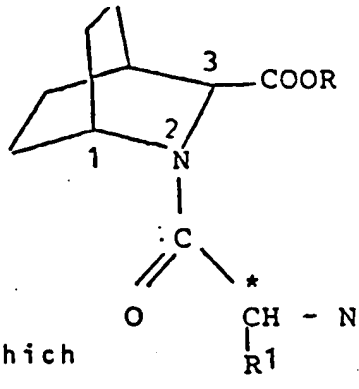
Example 31

N-(1-S-carboxy-3-cyclohexylpropyl)-S-lysyl-2-azabicyclo-[2.2.2]octane-3-S-carboxylic acid

m/e: 451 (M^+, 0.1%)

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I



(I),

in which

n denotes 0 or 1,

R denotes hydrogen, (C_1 to C_6)-alkyl or aralkyl having 7 to 9 carbon atoms,

R^1 denotes hydrogen or (C_1 to C_6)-alkyl which can optionally be substituted by amino, (C_1 to C_4)-acylamino or benzoylamino, (C_2 to C_6)-alkenyl, (C_5 to C_9)-cycloalkyl, (C_5 to C_9)-cycloalkenyl, (C_5 to C_7)-cycloalkyl-(C_1 to C_4)-alkyl, (C_6 to C_{10})-aryl or partially hydrogenated (C_6 to C_{10})-aryl, each of which can be substituted by (C_1 to C_4)-alkyl, (C_1 or C_2)-alkoxy or halogen, (C_6 to C_{10})-aryl-(C_1 to C_4)-alkyl or (C_7 to C_{11})-aroyl-(C_1 to C_4)-alkyl, both of which can be substituted, as defined above, in the aryl radical, a monocyclic or bicyclic heterocyclic radical having 5 to 7 or 8 to 10 ring atoms, 1 to 2 ring atoms of which represent sulfur or oxygen atoms and/or 1 to 4 ring atoms of which represent nitrogen atoms, or an optionally protected side chain of a naturally occurring α-aminoacid,

R^2 denotes hydrogen, (C_1 to C_6)-alkyl, (C_2 to C_6)-

alkenyl or (C_6 to C_{10})-aryl-(C_1 to C_4)-alkyl,

Y denotes hydrogen or hydroxyl,

Z denotes hydrogen or

Y and Z together denote oxygen and

X denotes (C_1 to C_6)-alkyl, (C_2 to C_6)-alkenyl, (C_5 to C_9)-cycloalkyl or (C_6 to C_{10})-aryl, which can be monosubstituted, disubstituted or trisubstituted by (C_1 to C_4)-alkyl, (C_1 to C_4)-alkoxy, hydroxyl, halogen, nitro, amino, (C_1 to C_4)-alkylamino, di-(C_1 to C_4)-alkylamino and/or methylenedioxy, or denotes 3-indolyl,

and also physiologically acceptable salts thereof.

2. A compound of the formula I as claimed in claim 1, wherein the carbon atom in position 3 of the bicyclic ring system and the carbon atoms marked with a star in the side chain have the S-configuration in each case.

3. A compound of the formula I as claimed in claim 1 or 2, in which

n denotes 1,

R denotes hydrogen or (C_1 to C_4)-alkyl,

R^1 denotes hydrogen, (C_1 to C_3)-alkyl, the optionally acylated side chain of lysine, (C_2 or C_3)-alkenyl, benzyl, the O-(C_1 to C_6)-alkylated side chain of tyrosine, phenethyl, 4-aminobutyl or benzoylmethyl,

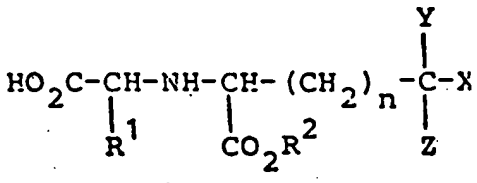
R^2 denotes hydrogen, (C_1 to C_4)-alkyl or benzyl and

X denotes cyclohexyl or phenyl which can be monosubstituted or disubstituted or, in the cas of

methoxy, trisubstituted by (C_1 or C_2)-alkyl, (C_1 or C_2)-alkoxy, hydroxyl, fluorine, chlorine, bromine, amino, (C_1 to C_4)-alkylamino, di-(C_1 to C_4)-alkylamino, nitro and/or methylenedioxy.

4. A process for the preparation of a compound of the formula I as claimed in any of claims 1 to 3, which comprises

a) reacting a compound of the formula II

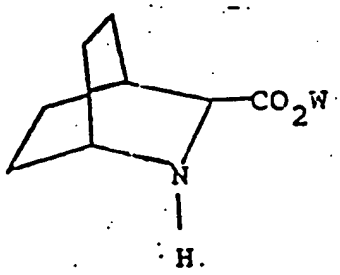


(II),

in which

n, R^1, R^2, X, Y and Z have the same meaning as in formula I,

with a compound of the formula III



(III),

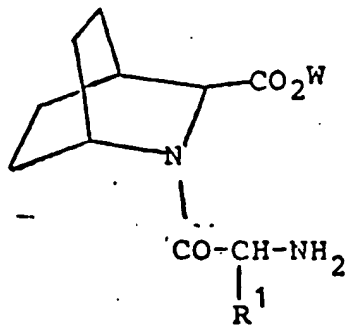
in which

W denotes hydrogen or a radical which can be split off under acid conditions or by hydrogenolysis,

and, if appropriate, subsequently splitting off W and/or R^2 with the formation of the free carboxyl groups, or

b) in order to prepare a compound of the formula I in which Y and Z together denote oxygen,

b_1) reacting a compound of the formula IV.



(IV),

in which

R^1 has the same meaning as in formula I and

W has the same meaning as in formula III,

with a compound of the formula V

$$R^2O_2C\text{-}CH{=}CH\text{-}CO\text{-}X \qquad (V),$$

in which

R^2 and X have the same meanings as in formula I, and, if appropriate, subsequently splitting off W and/or R^2 with the formation of the free carboxyl groups, or

b_2) reacting a compound of the formula IV mentioned under b_1) with a compound of the general formula VI in which R^2 has the same meaning as in formula I, and with a compound of the general formula VII

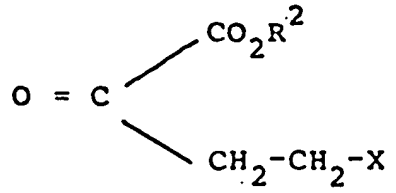
$OHC\text{-}CO_2R^2$ (VI) $\qquad$ $X\text{-}CO\text{-}CH_3$ (VII)

in which

X has the same meaning as in formula I,

and, if appropriate, subsequently splitting off W and/or R^2 with the formation of the free carboxyl groups, or

c) in order to prepare a compound of the formula I in which Y and Z each denote hydrogen, reacting a compound of the formula IV mentioned under b_1) with a compound of the formula VIII



(VIII),

in which

R^2 and X have the same meanings as in formula I, reducing the resulting Schiff's base and, if appropriate, subsequently splitting W and/or R^2 with the formation of the free carboxyl groups, or

d) in order to prepare a compound of the formula I in which Y denotes hydroxyl and Z denotes hydrogen, reducing a compound of the formula I in which Y and Z together denote oxygen with a complex boranate or a borane-amine complex,

converting, if appropriate, a compound of the formula I which has been obtained in accordance with a) to d) and in which R represents hydrogen, into an ester of the formula I in which R denotes (C_1 to C_6)-alkyl or (C_7 to C_9)-aralkyl, and, if appropriate, converting a compound of the formula I into its physiologically acceptable salt.

5. The use of a compound as claimed in any of claims 1 to 3 as a medicine.

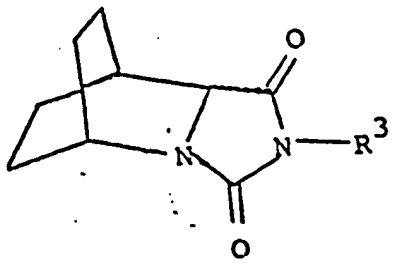
6. A compound as claimed in any of claims 1 to 3 for use as a medicine.

7. An agent containing a compound as claimed in any of claims 1 to 3.

8. A compound of the formula III in which W has the meaning defined in claim 4.

9. A process for the preparation of a compound of the formula III as claimed in claim 8, which comprises

a) saponifying a compound of the formula IX



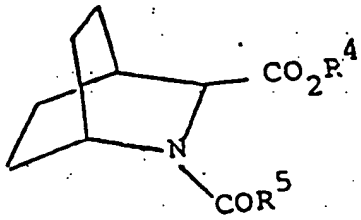
(IX),

in which

R^3 represents a (C_1-C_6)-alkyl, aryl-(C_1-C_3)-alkyl, phenyl, 4-methoxyphenyl or 4-chlorophenyl radical,

by means of an alkali metal hydroxide or alkaline earth metal hydroxide, in water or mixtures thereof with an organic solvent, and, if appropriate, esterifying the resulting aminoacid (III/W = hydrogen) in accordance with customary methods of aminoacid chemistry, or

b) reacting a compound of the formula X



(X),

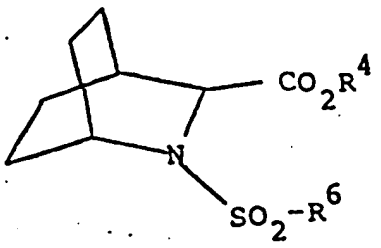
in which

R^4 denotes a $(C_1$ to $C_6)$-alkyl or aryl-(C_1-C_3)-alkyl radical and

R^5 denotes a phenyl, methyl, $(C_1$ to $C_4)$-alkoxy or aryl-$(C_1$ to $C_3)$-alkoxy radical,

with an alkali metal hydroxide or alkaline earth metal hydroxide under the conditions of variant a) and, if appropriate, esterifying the resulting aminoacid (III, W = hydrogen), or

c) reacting a compound of the formula XI



(XI),

in which

R^4 has the same meaning as in formula X and

R^6 represents a phenyl, 4-methylphenyl or 4-chlorophenyl radical,

first with an alkali metal or alkaline earth metal, in liquid ammonia at -60°C to -10°C, and then with an alkali metal hydroxide or alkaline earth metal hydroxide at 20° to 120°C, in particular 60 to 100°C, and, if appropriate, esterifying the product, or reversing the sequence of the reaction stages described.

10. The use of a compound as claimed in any of claims 1 to 3 as a medicine in combination with a diuretic.

11. An agent containing a compound as claimed in any of claims 1 to 3, in combination with a diuretic.

DATED this 5th day of July 1983.

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